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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,673	01/16/2004	Danila Valmori	LUD 5483.7 DIV (10316191)	7395

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	
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09/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,673	VALMORI ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,21 and 24-31* is/are pending in the application.

4a) Of the above claim(s) *27-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19, 21, 24, 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed 5/7/08 is acknowledged and has been entered.

2. Applicant has amended claim 19 to recite SEQ ID NO: 7, 8, 10, 11 and 16 in addition to the elected species SEQ ID NO: 9. Since 112, 1st paragraph issues remain with regard to SEQ ID NO: 9, the search has not been extended to include other recited peptide species.

Therefore, claims 27-31 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 19, 21 and 24-26 are being examined as they read on the elected species, SEQ ID NO: 9.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 19, 21 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the originally filed disclosure is as follows: "taken from a patient with a tumor" in the context of base claim 19.

Applicant argues in the said amendment (on page 4) that Applicant has support for tumor infiltrating lymphocytes which de facto means the patient has a tumor.

However, the disclosure in the instant specification is that tumor infiltrating lymphocytes (TILs) were generated from tumor invaded lymph nodes of patients with melanoma who were HLA-A*0201 positive, the TILs being LAU203 and LAU132 and CTL lines from melanoma patient's PBMCs being LAU145, LAU86, LAU50, LAU148, LAU161 and LAU119 as evidenced by evidentiary reference Valmori *et el* (J. Immunol. 1998, 160: 1750-1758, of record). Thus, support exists only for a sample containing CTL precursors taken from a melanoma patient.

5. Claims 19, 21, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing proliferation of CTLs, comprising contacting a sample from melanoma patients (*i.e.,* humans with melanoma) with (i) a polytope, wherein said polytope comprises the amino acid sequence set forth in SEQ ID NO: 9, wherein said amino acid sequence forms a complex with an HLA molecule, including HLA-A2, and (ii) a sample of cells which present HLA molecules on their surfaces and which process said polytope to Melan-A peptides which complex with said HLA molecules, wherein the complexes of said HLA molecules and the amino acid sequence of SEQ ID NO: 9 induce proliferation of CTLs, does not reasonably provide enablement for the claimed method wherein the sample containing CTLs is not from a melanoma patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's amendment of instant base claim 19 and the addition of new claims 25 and 26 have necessitated this new ground of rejection.

The specification discloses at [0109] "Polytopes are groups of two or more potentially immunogenic or immune stimulating peptides, which can be joined together in various ways, to determine if this type of molecule will stimulate and/or provoke an immune response." The specification at [0111] discloses "Also, a feature of the invention is the use of these peptides to determine the presence of cytolytic T cells in a sample. It was shown, supra, that CTLs in a sample will react with peptide/MHC complexes. Hence, if one knows that CTLs are in a sample, HLA-A2 positive cells can be "lysed" by adding the peptides of the invention to HLA-A2 positive cells, such as HLA-A*0201 positive cells, and then determining, e.g., radioactive chromium release, TNF production, etc. or any other of the methods by which T cell activity is determined. Similarly, one can determine whether or not specific tumor infiltrating lymphocytes ("TILs") are present in a sample, by adding one of the claimed peptides with HLA-A2 positive cells to a sample, and determining lysis of the HLA-A2 positive cells via, e.g., ^{51}Cr release, TNF presence and so forth. The specification at [0112] discloses "Of course, the peptides may also be used to provoke production of CTLs. As was shown, supra, CTL precursors develop into CTLs when confronted with appropriate complexes. By causing such a "confrontation" as it were, one may generate CTLs. This is useful in an in vivo context, as well as ex vivo, for generating such CTLs." In Example 6, the instant specification discloses that peripheral blood lymphocytes from HLA-A2 positive melanoma patients were purifed, enriched for CD8+ T cells , incubated with peripheral blood lymphocytes that were incubated with melanoma peptides, including SEQ ID NO: 9, and CTL activity was assayed.

The specification further discloses at [0013] "The preceding survey of the relevant literature shows that various peptides, usually eight, nine, or ten amino acids in length, complex with MHC molecules and present targets for recognition by cytolytic T cells. A great deal of study has been carried out on melanoma, and melanoma antigens which are recognized by cytolytic T cells are now divided into three broad categories. The first, which includes many of the antigens discussed, supra, (e.g., MAGE), are expressed in some melanomas, as well as other tumor types, and normal testis and placenta. The antigens are the expression product of normal genes which are usually silent in normal tissues. [0014] A second family of melanoma antigens includes antigens which are derived from mutant forms of normal proteins. Examples of this family are MUM-1 … A third category, also discussed, supra, includes the differentiation antigens which are expressed by both melanoma and melanocytes. Exemplary are tyrosinase, gp100, gp75, and Melan A/Mart-1."

The specification at [0015] discloses "Cytolytic T cells ("CTLs" hereafter) have been identified in peripheral blood lymphocytes, and tumor infiltrating lymphocytes, of melanoma patients who are HLA-A*0201 positive."

Evidentiary reference Janeway-Travers (Immunobiology. 1994, pages 7.3-7.4, Garland Publ., Inc., NY and London, of record) teach "…only one naïve T cell in 10^5 is likely to be specific for a particular antigen…" (page 7.3 at the last paragraph), thus indicating that T cells are specific for a particular antigenic peptide and that the frequency of naive T cells able to react with a particular antigen is extremely low.

The instant claims recite the mixing of a polytope peptide with a sample containing CTL precursors, *i.e.,* naïve T cells that are not primed by antigen, T cells that are very low in frequency as evidenced by Janeway-Travers supra. The scope of the claim encompasses mixing the polytope peptide with a sample a patient with a tumor wherein said patient does not have CTLp specific for SEQ ID NO: 9.

In addition, the instant claims recite that a sample of cells that present HLA molecules on their surfaces process the polytope to Melan-A peptides which complex with the HLA molecules, and wherein the complexes of the said HLA molecules and the amino acid sequence of SEQ ID NO: 9 (ELAGIGILTV) induce proliferation of CTL. The specification does not disclose this process for any other HLA molecule except for HLA-A*-0201.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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August 21, 2008

/G.R. Ewoldt/
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